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(71) Applicant *(for all designated States except US)*: ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BRATTSAND, Ralph [SE/SE]; Skolmästarvägen 4, S-224 67 Lund (SE). HOLMDAHL, Rikard [SE/SE]; Siriusgatan 2, S-224 57 Lund (SE). JANSSON, Liselotte [SE/SE]; Stortorget 5, S-222 23 Lund (SE). LONCAR, Marjana [SE/SE]; Stora Södergatan 42, S-222 23 Lund (SE). PETTERSSON, Lars [SE/SE]; Näktergalsvägen 33, S-247 36 Södra Sandby (SE).

(74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).

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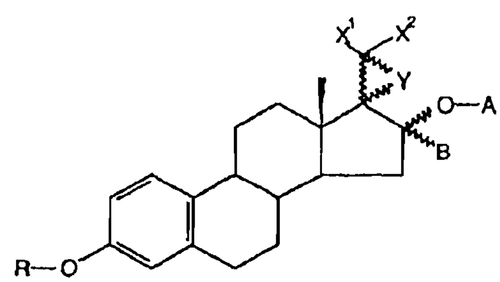
(54) Title: NOVEL ESTROGENS

(57) Abstract

Compounds of formula (I), a process for their preparation, their use in the treatment of autoimmune disorders as well as new intermediates for their preparation.



(I)

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NOVEL ESTROGENS

Field of the invention

The present invention relates to novel compounds which are steroidal estrogens, to methods for their preparation, their use and pharmaceutical compositions comprising the novel compounds. The novel compounds are useful for the treatment of inflammatory and imn.unologic disorders, especially for the treatment of autoimmune disorders. The compounds according to the present invention are especially preferred for the treatment of rheumatoid arthritis (RA) and multiple sclerosis (MS).

Background and prior art

Sex hormones have since long been known to ameliorate arthritic symptoms in chronic arthritis during pregnancy, see for example Hench P.S. "The ameliorating effect of pregnancy on chronic atrophic arthritis, fibrositis, and intermittent hydrathrosis", Mayo Clin. Proc., 13, 161-167, 1938. The use of oral contraceptives in patients with rheumatoid arthritis (RA) have proven to decrease the incidence of RA, see Wingrave S.J., Kay C.R. "Reduction in incidence of rheumatoid arthritis associated with oral contraceptives", Lancet, 569-571, 1978; Vandenbroucke J.P. et al., "Oral contraceptives and rheumatoid arthritis: Further evidence for a preventive effect", Lancet 839-842, 1982.

In JP 268575/ 1990 estradiol derivatives are described, but the substituents in 17-position are completely different from the substituents in 17-position of the present application. The problem underlying the invention described in JP 268575/ 1990 is to find compounds against osteoporosis, said compounds having an excellent bone resorption inhibiting action without showing side effects such as risk for genital cancer etc. known in the art for estrogens.

The problem underlying the present invention is to develop novel steroidal estrogens with high anti-inflammatory and immunosuppressive effects, but with low "sex hormonal" activities. The steroidal estrogens known in the prior art, have the disadvantages that they influence genital and breast tissues, thereby conferring adverse effects such as endometrial and breast cancers if given in too high amounts.

The problem mentioned above has been solved by developing new steroidal estrogens according to the formula I, as will be described in the following.

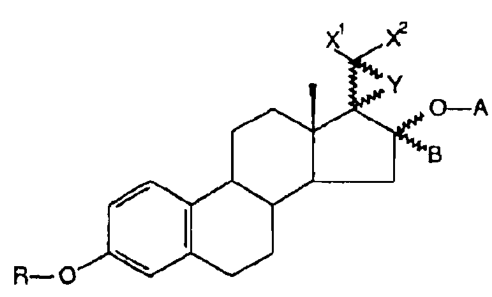
Outline of the invention

The object of the present invention is to provide novel compounds, which are steroidal estrogens, and a method for their preparation.

Another object of the present invention is the use of the novel compounds for the treatment of inflammatory and immunologic diseases, especially for the treatment of autoimmune diseases.

Still another object of the invention is a pharmaceutical composition comprising a compound of the invention as active ingredient, optionally in the presence of a pharmaceutically acceptable carrier.

The novel compounds of the present invention are defined by the general formula I



I

wherein

A is hydrogen, C_2-C_{18} alkanoyl, (C_6 aryl)carbonyl, C_2-C_{19} alkoxycarbonyl, (C_6 aryloxy)carbonyl, or a protecting group;

B is hydrogen, methyl, or ethyl;

R is hydrogen, a straight, branched or cyclic C_1-C_6 alkyl, C_2-C_{18} alkanoyl, (C_6 aryl)carbonyl, C_2-C_{19} alkoxycarbonyl, (C_6 aryloxy)carbonyl, or a protecting group;

X^1 is hydrogen, methyl, ethyl, or halogen;
X^2 is hydrogen, methyl, ethyl, or halogen; and

Y is methylene or a single bond;

the compounds

(17E)-16α-Acetoxy-3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraene;
(17E)-16α-Hydroxy-3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraene;
(17E)-16β-Hydroxy-3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraene;

being excluded.

Within the scope of the invention are also pharmaceutically acceptable salts of the compounds of the formula I.

Preferred compounds of the invention are compounds of the formula I wherein

A is hydrogen, or C_2-C_6 alkanoyl;
B is hydrogen, or methyl;

R is hydrogen, a straight, branched or cyclic C_1-C_6 alkyl, C_2-C_{18} alkanoyl, (C_6 aryl)carbonyl , C_2-C_{19} alkoxycarbonyl, (C_6 aryloxy)carbonyl, or a protecting group;

X[1] is hydrogen, methyl, or fluorine;
X[2] is hydrogen, methyl, or fluorine; and
Y is methylene or a single bond.

Particularly preferred compounds of the invention are compounds according to the formula I wherein

A is hydrogen or C_2-C_6 alkanoyl;
B is hydrogen;
R is hydrogen, a straight, branched or cyclic C_1-C_6 alkyl, C_2-C_{19} alkanoyl or (C_6 aryl)carbonyl;
X[1] is hydrogen, or fluorine;
X[2] is hydrogen, or fluorine; and
Y is a single bond or a methylene group.

Examples of protecting groups are benzyl, THP (tetrahydropyranyl), methoxymethyl, dimethylthexylsilyl, and tert-butyldimethylsilyl. A preferred protecting group is dimethylthexylsilyl.

The most preferred compound of the invention is 3,16α-dihydroxy-17-methylene-estra-1,3,5(10)triene.

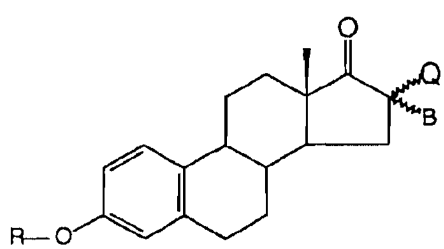
The novel steroidal estrogens according to the invention are characterized by high anti-inflammatory and immunosuppressive effects, and low "sex hormonal" activities. Thus the novel steroidal estrogens have low proliferative effects on genital tissues which reduce the possible adverse effects such as endometrial cancers.

The novel steroidal estrogens according to the invention are useful for the treatment of inflammatory and immunologic disorders, especially for the treatment of autoimmune disorders.

The steroidal estrogens according to the present invention are excellent for the treatment of rheumatoid arthritis (RA) and multiple sclerosis (MS).

Methods of preparation

Common to all starting materials for the preparation of compounds of the formula I is the presence of a 17-keto group. The introduction of the 17-alkylidene group can be achieved by a Wittig-type reaction (see e.g. Krubiner, A. M. *et al.* J. Org. Chem., 1966, 31, 24) whereby a compound of the formula II



II

wherein

A is hydrogen, C_2-C_{18} alkanoyl, C_6 aroyl, C_2-C_{19} alkoxycarbonyl, (C_6 aryloxy)carbonyl, or a protecting group;

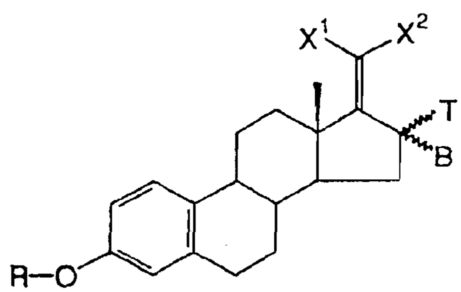
B is hydrogen, methyl, or ethyl;

R is hydrogen, a straight, branched or cyclic C_1-C_6 alkyl, C_2-C_{18} alkanoyl, (C_6 aryl)carbonyl, C_2-C_{19} alkoxycarbonyl, (C_6 aryl)oxycarbonyl, or a protecting group; and

Q is (O-A) or hydrogen, wherein O is oxygen and A is as defined above;

the 3-O-position being optionally protected

is reacted with a phosphorous ylide or with the salt of a stabilized alkylphosphonate, optionally followed by the reduction of the adduct when a stabilized alkyl phosphonate is used, giving a compound of the formula III



III

wherein

A is hydrogen, C_2-C_{18} alkanoyl, C_6 aroyl, C_2-C_{19} alkoxycarbonyl, (C_6 aryloxy)carbonyl, or a protecting group;

B is hydrogen, methyl, or ethyl;

R is hydrogen, a straight, branched or cyclic C_1-C_6 alkyl, C_2-C_{18} alkanoyl, (C_6 aryl)carbonyl, C_2-C_{19} alkoxycarbonyl, (C_6 aryloxy)carbonyl, or a protecting group; and

$\mathbf{X^1}$ is hydrogen, methyl, ethyl or halogen; and
$\mathbf{X^2}$ is hydrogen, methyl, ethyl or halogen.

T is (O-A) or hydrogen, wherein O is oxygen and A is as defined above;

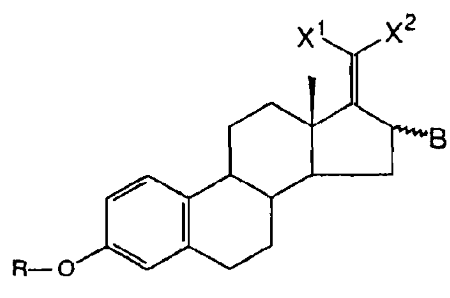
the 3-O-position being optionally protected.

The above given definition that Q and T is (O-A) or hydrogen respectively, means that the 16-position may be protected or unprotected.

The reaction is preferably carried out in a polar solvent such as DMSO, THF or *dimethoxyethane, and the temperature is preferably in the range ambient temperature to the* boiling point of the solvent.

When stabilized alkylphosphonates are used, the substituents X^1 and X^2 in formula III may be carbonyl moieties, such as an ester or ketone, which can be reduced to an alcohol, and further reduced to an alkyl group.

The 16-OA functionality may be present in the starting material or introduced at a later stage. If not present in the starting material, the 16-OA functionality is introduced via an oxidation such as a SeO_2-oxidation (Sharpless, K. B. *et al.* Aldrichimica Acta, 1979, 12, 63), whereby a compound of the formula IV



IV

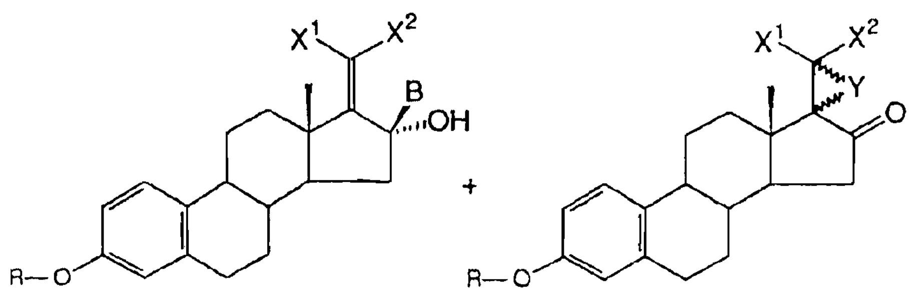
wherein

B is hydrogen, methyl, or ethyl;

R is hydrogen, a straight, branched or cyclic C_1-C_6 alkyl, C_2-C_{18} alkanoyl, (C_6 aryl)carbonyl, C_2-C_{19} alkoxycarbonyl, (C_6 aryloxy)carbonyl, or a protecting group; and

X^1 and X^2 is each and independently hydrogen, methyl, or ethyl;

is subjected to a SeO_2-oxidation, giving the 16α-OH compound of the formula V selectively (Trost, B. M. *et al.* J. Am. Chem. Soc., 1978, 100, 3435) together with the 16-keto compound of the formula VI



V VI

wherein

B is hydrogen, methyl, or ethyl;

R is hydrogen, a straight, branched or cyclic C_1-C_6 alkyl, C_2-C_{18} alkanoyl, (C_6 aryl)carbonyl, C_2-C_{19} alkoxycarbonyl, (C_6 aryloxy)carbonyl, or a protecting group;

$\mathbf{X^1}$ and $\mathbf{X^2}$ is each and independently hydrogen, methyl or ethyl; and
Y is a single bond.

In a compound of the formula VI, X^1 and X^2 may also each and independently be selected from a halogen, and Y may also be selected from methylene.

SeO_2 is preferably used in catalytic amounts together with tertbutylhydroperoxide as a co-oxidant in toluene at ambient temperature.

These first reaction steps can be performed on either 3-O-unprotected (R=H) or protected (R= e.g. R_3Si, tetrahydropyranyl (THP), alkyl, benzyl) material. The introduction of the protecting group is achieved by standard methods (Protective groups in organic synthesis, Green, T.W. and Wuts, P.G.M., 2nd ed., Wiley). Thus, the free phenol can be protected as a dimethyl-thexylsilyl ether using dimethyl-thexylsilyl chloride as silylating reagent and imidazole as base in the solvent dimethylformamide (DMF) at ambient temperature.

The 16-keto compound of the formula VI is further subjected to a nucleophile, such as a Grignard reagent in an inert solvent, such as Et_2O or THF, or alternatively reduced, e.g. with $NaBH_4$ or $LiAlH_4$, giving the 16β-hydroxy compound of the formula I wherein Y is a single bond.

The cyclopropane moiety is introduced by reacting a compound of the formula I or VI with a cyclopropanation reagent, whereby the alkene moiety of the compound of the formula I or VI wherein Y is a single bond, is reacted with a cyclopropanation reagent, optionally in the presence of a metal promotor, giving a compound of the formula I or of the formula VI (Y=methylene) respectively. One preferred cyclopropanation reaction is the Simmons-Smith reaction, using a

1,1-dihalo compound in the presence of activated Zn, preferably in etheral solvents such as dimethoxyethane. The cyclopropanation reaction of choice for the introduction of the cyclopropane moiety will be clear for the man skilled in the art (Advanced Organic Chemistry: reactions, mechanisms and structure, J. March, 4th ed., p 870 ff., Wiley).

The phenolic 3-OH group may be protected, e.g. as a silylether (or as alkylether, benzylether or as an acetal, like THP-ether) throughout the reaction sequences. Thus, the unprotected 16-OH can then be reacted with activated ester derivatives, such as ester halides or anhydrides, to give 16-O-monoacylated derivatives.

The 3-O-silyl ether can be cleaved by fluoride ion (e.g. $Bu_4NF\ (H_2O)_3$ in THF) or by acid or base treatment to give the free phenol derivatives (van Look , G., "Silylating Agents",

Fluka Chemie, 1988). The 3-O-monoacylated derivatives can also be regioselectively prepared, e.g. by acylating the tetrabutylammonium phenolate generated in the Bu_4NF-desilylation step by acylatating agents like acid chlorides or anhydrides, or by acylating the 3,16-diol by the method of Illi V.O., Tetrahedron Lett. 1979, p. 2431using acid chlorides as acylating reagents in dioxane, NaOH as base and catalytic amounts of tetrabutylammonium hydrogen sulfate.

Examples

The invention will now be described in more detail by the following examples which are not to be construed as limiting the invention.

In the examples column chromatography separations were performed using Merck SiO_2 60 (0.040-0.063 mm) silica gel with heptane-EtOAc mixtures as eluents.

TLC analyses were performed on Merck SiO_2 60 F254 precoated aluminium sheets: R_f values were measured in heptane-EtOAc eluent mixtures and the spots were visualized by charring with 10% aqueous H_2SO_4.

Melting points were determined with a Weitz Wetzlar microscope and are uncorrected.

MS(FAB) spectra were recorded with a VG Analytical Autospec-Q spectrometer.

NMR spectra were recorded with a Varian VXR (300 MHz) or a Varian Unity+ (500 MHz).

Dry solvents were prepared by drying p.a. (pro analysis) grade solvents over molecular sieves (4Å).

General procedure for 16α-hydroxylation of 17-alkylidenes (Procedure A):

SeO_2 (11 mg, 0.1 mmol) was added to a solution of the 17-alkylidene (1.0 mmol) and tert-butylhydroperoxide (0.67 ml, ca 2.0 mmol, ca 3.0 M "phase separated" in toluene, Sharpless, K. B. *et al.* Aldrichimica Acta, 1979, 12, 63) in toluene (1.0 ml). The reaction mixture was stirred over night and thereafter diluted with Et_2O (50 ml). $FeSO_4$ (10 ml, 1 M) was added and after 30 min stirring the organic phase was separated and washed with brine (2 x 30 ml). The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. The residue was purified by column chromatography to give the 17-alkylidene-16α-hydroxy compound (yields ca 40-60 %) and the 17-alkylidene-16-keto compound (yields ca 20-30 %).

General procedure for 3-O-desilylation of 3-O-dimethyl-thexylsilyl ether protected 3-hydroxy-estra-1,3,5(10)-trienes (Procedure B):

$NBu_4F{\cdot}(H_2O)_3$ (1.1 mmol) was added to a solution of the 3-dimethyl-thexylsilyl ether protected 3-hydroxy-estra-1,3,5(10)-triene (1.0 mmol) in dry THF (1.0 mL). The reaction mixture was stirred for 3 min and thereafter quenched by adding AcOH (1.5 mmol). Concentration at reduced pressure was followed by purification on column chromatography. Alternatively, for larger scale synthesis usual work up (dilution with Et_2O, washing with water, drying, and concentration) may precede the column chromatography.

Silylations were performed according to the Corey procedure (Corey, E. J., Venkateswarlu, A. *J. Am. Chem. Soc.* 1972, 94, 6190) with dimethyl-thexyl chlorosilane (1.2 mol eq.) as silylating agent and imidazole (2.5 mol eq.) as base in DMF as solvent. Usual work-up (dilution with Et_2O, washing with water, drying, and concentration) followed by column chromatography provided the products in essentially quantitative yields.

Example 1 - 2

3,16α-Dihydroxy-17-methylene-estra-1,3,5(10)-triene

Prepared from 3-hydroxy-17-methylene-estra-1,3,5(10)-triene (83% from estrone, Peters, R. H. *et al.* J. Med. Chem. 1989, 32, 1642) according to Procedure A .

Also prepared from 3,16α-dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3-dimethyl-thexylsilyl ether (Example 5) according to Procedure B.

Yield: 356 mg (92 %)

R_f (2:1)=0.20

mp 245-50°C

MS(FAB): m/z = 284 (M^+)

^{1}H NMR ($CDCl_3$) δ 0.83 (s, 3H, H-18), 4.53 (s, 1H, phenol), 4.72 (m, 1H, H-16), 4.93 (d, 1H, J=2.1 Hz, $=CH_2$), 5.08 (d, 1H, J=1.4 Hz, $=CH_2$), 6.57 (d, 1H, J=2.8 Hz, H-4), 6.63 (dd, 1H, J=2.8 Hz, 8.3 Hz, H-2), 7.17 (d, 1H, J=8.3 Hz, H-1)

Example 3

3-Hydroxy-17-keto-estra-1,3,5(10)-triene, 3-O-dimethylthexylsilyl ether

Prepared from 3-hydroxy-17-keto-estra-1,3,5(10)-triene (estrone) by silylation using the Corey procedure.

Yield: 29.3 g (94 %)

R_f (10:1)=0.10

^{1}H NMR ($CDCl_3$) δ 0.22 (s, 6H, $-SiMe_2-$), 0.91 (s, 3H, H-18), 0.94 (s, 6H, thexyl), 0.94 (d, 6H, J=6.6 Hz, thexyl), 6.56 (d, 1H, J=2.7 Hz, H-4), 6.62 (dd, 1H, J=2.7 Hz, 8.3 Hz, H-2), 7.12 (d, 1H, J=8.3 Hz, H-1)

Example 4

3-Hydroxy-17-methylene-estra-1,3,5(10)-triene, 3-O-dimethylthexylsilyl ether

Prepared from 3-hydroxy-17-methylene-estra-1,3,5(10)-triene (83% from estrone, Peters, R. H. *et al.* J. Med. Chem. 1989, 32, 1642) by silylation using the Corey procedure.

Yield: 22.4 g (99 %)

R_f (8:1)=0.18

^{1}H NMR ($CDCl_3$) δ 0.22 (s, 6H, -$SiMe_2$-), 0.82 (s, 3H, H-18), 0.94 (s, 6H, thexyl), 0.94 (d, 6H, J=6.6 Hz, thexyl), 4.67 (s, 2H, =CH_2), 6.55 (d, 1H, J=2.8 Hz, H-4), 6.61 (dd, 1H, J=2.8 Hz, 8.3 Hz, H-2), 7.14 (d, 1H, J=8.3 Hz, H-1)

Example 5

3,16α-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3-O-dimethyl-thexylsilyl ether

Prepared from 3-hydroxy-17-methylene-estra-1,3,5(10)-triene, 3-O-dimethyl-thexylsilyl ether according to procedure A.

Yield: 5.07 g (59 %)

R_f (5:1)=0.29

^{1}H NMR ($CDCl_3$) δ 0.22 (s, 6H, -$SiMe_2$-), 0.83 (s, 3H, H-18), 0.94 (s, 6H, thexyl), 0.94 (d, 6H, J=6.6 Hz, thexyl), 4.71 (m, 1H, H-16), 4.92 (d, 1H, J=2.2 Hz, =CH_2), 5.08 (d, 1H, J=1.7 Hz, =CH_2), 6.55 (d, 1H, J=2.7 Hz, H-4), 6.61 (dd, 1H, J=2.7 Hz, 8.3 Hz, H-2), 7.13 (d, 1H, J=8.3 Hz, H-1)

This reaction also provided the compound of Example 6 below.

Example 6

3-Hydroxy-16-keto-17-methylene -estra-1,3,5(10)-triene, 3-O-dimethyl-thexylsilyl ether

See under Example 5 regarding the synthesis.

Yield: 1.54 g (18 %)

R_f (5:1)=0.56

^{1}H NMR ($CDCl_3$) δ 0.22 (s, 6H, $-SiMe_2-$), 0.94 (s, 6H, thexyl), 0.94 (d, 6H, J=7.0 Hz, thexyl), 0.99 (s, 3H, H-18), 5.07 (s, 1H, $=CH_2$), 5.84 (s, 1H, $=CH_2$), 6.56 (d, 1H, J= 2.5 Hz, H-4), 6.63 (dd, 1H, J=2.5 Hz, 8.3 Hz, H-2), 7.13 (d, 1H, J=8.3 Hz, H-1)

Example 7

3,16β-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3-O-dimethylthexylsilyl ether

$CeCl_3$ (283 mg, 1.15 mmol) was added to a solution of 3-hydroxy-17-methylene-16-keto-estra-1,3,5(10)-triene, 3-dimethyl-thexylsilyl ether (488 mg, 1.15 mmol) in dry THF (12ml) under N_2. The slurry was stirred for 5 min and then $LiAlH_4$ (44 mg, 1.15 mmol) was added. The reaction mixture was stirred at room temperature for 15 min, then quenched with 1 M HCl and partitioned in Et_2O/water. The organic phase was washed with aq. $NaHCO_3$ (sat.) and brine, dried over Na_2SO_4 and concentrated at reduced pressure. The residue was purified by column chromatography (heptane-EtOAc, 5:1) to give the titel compound (220 mg, 45 %) as a white solid.

R_f (5:1)=0.16

^{1}H NMR ($CDCl_3$) δ 0.22 (s, 6H, $-SiMe_2-$), 0.94 (s, 6H, thexyl), 0.94 (d, 6H, J=7.0 Hz, thexyl), 1.00 (s, 3H, H-18), 4.55 (m, 1H, H-16), 4.92 (s, 1H, $=CH_2$), 5.08 (s, 1H, $=CH_2$), 6.55 (d, 1H, J= 2.7 Hz, H-4), 6.61 (dd, 1H, J=2.7 Hz, 8.3 Hz, H-2), 7.13 (d, 1H, J=8.3 Hz, H-1)

Example 8

3,16β-Dihydroxy-17-methylene-estra-1,3,5(10)-triene

Prepared from 3-hydroxy-17-methylene-estra-1,3,5(10)-triene, 3-O-dimethyl-thexylsilyl ether according to procedure B.

Yield: 46 mg (85 %)

R_f (1:1)=0.42

mp 229-35°C

MS(FAB): m/z = 284 (M^+)

^{1}H NMR ($CDCl_3$) δ 1.00 (s, 3H, H-18), 4.53 (m, 1H, H-16), 4.94 (d, 1H, J=1.8 Hz, =CH_2), 5.08 (d, 1H, J=1.8 Hz, =CH_2), 6.56 (d, 1H, J=2.7 Hz, H-4), 6.64 (dd, 1H, J=2.7 Hz, 8.5 Hz, H-2), 7.16 (d, 1H, J=8.5 Hz, H-1)

Example 9

3,16β-Dihydroxy-16α-methyl-17-methylene-estra-1,3,5(10)-triene, 3-O-dimethyl--thexylsilyl ether

A solution of 3-hydroxy-17-methylene-16-keto-estra-1,3,5(10)-triene, 3-dimethyl-thexylsilyl ether (108 mg, 0.25 mmol) in dry Et_2O (2mL) was added to MeMgI (1 mmol, 1M in Et_2O) at 0°C under N_2. The reaction mixture was stirred at room temperature over night, then quenched with 1 M HCl and partitioned in Et_2O/water. The organic phase was washed with aq. $NaHCO_3$ (sat.) and brine, dried over Na_2SO_4 and concentrated at reduced pressure. The residue was purified by column chromatography (heptane-EtOAc, 8:1) to give the titel compound (40 mg, 37%) as a white solid.

R_f (5:1)=0.21

^{1}H-NMR ($CDCl_3$) δ 0.22 (s, 6H, -$SiMe_2$-), 0.94 (s, 6H, thexyl), 0.94 (d, 6H, J=7.0 Hz, thexyl), 1.03 (s, 3H, H-18), 1.41 (s, 3H, 16-Me), 4.82 (s, 1H, =CH_2), 5.06 (s, 1H, =CH_2), 6.55 (d, 1H, J= 2.7 Hz, H-4), 6.61 (dd, 1H, J=2.7 Hz, 8.3 Hz, H-2), 7.11 (d, 1H, J=8.3 Hz, H-1)

Example 10

3,16β-Dihydroxy-16α-methyl-17-methylene-estra-1,3,5(10)-triene

Prepared from 3,16β-dihydroxy-16α-methyl-17-methylene-estra-1,3,5(10)-triene, 3-O-dimethyl-thexylsilyl ether according to procedure B.

Yield: 12 mg (93 %)

R_f (2:1)=0.22

mp 237-39°C

MS-FAB: m/z = 298 (M^+)

^{1}H NMR ($CDCl_3$) δ 1.03 (s, 3H, H-18), 1.41 (s, 3H, 16-Me), 4.51 (s, 1H, phenol), 4.83 (s, 1H, =CH_2), 5.07 (s, 1H, =CH_2), 6.57 (d, 1H, J= 2.8 Hz, H-4), 6.63 (dd, 1H, J=2.8 Hz, 8.3 Hz, H-2), 7.16 (d, 1H, J=8.3 Hz, H-1)

<u>Example 11</u>

<u>3,16α-Dihydroxy-17-(1',2'-ethylene)-estra-1,3,5(10)-triene, 3-O-dimethyl-thexylsilyl ether</u>

A slurry of Zn powder (280 mg, 4.28 mmol) in dry dimethoxyethane (DME, 4.0 ml) under N_2 was activated by ultra sound treatment for 1.5 h. A solution of 3,16α-dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3-O-dimethyl-thexylsilyl ether (500 mg, 1.17 mmol) in dry DME (8.0 mL) was added and the temperature was raised to reflux temperature (ca 90°C in oil bath). CH_2I_2(390 mL, 4.83 mmol) was added dropwise and the reaction mixture was stirred at reflux temperature over night. After cooling the reaction mixture was partitioned in EtOAc/NH_4Cl (aq., sat.). The organic phase was washed with H_2O, dried over Na_2SO_4 and concentrated at reduced pressure. The residue was purified by column chromatograph (heptane-EtOAc, 8:1) to give the title compound (280 mg, 54 %).

R_f (5:1)=0.28

^{1}H NMR ($CDCl_3$) δ 0.22 (s, 6H, -$SiMe_2$-), 0.50, 0.72 (2m, 4H, 17-ethylene), 0.82 (s, 3H, H-18), 0.94 (s, 6H, thexyl), 0.94 (d, 6H, J=7.0 Hz, thexyl), 4.19 (m, 1H, H-16), 6.56 (d, 1H, J= 2.7 Hz, H-4), 6.62 (dd, 1H, J=2.7 Hz, 8.3 Hz, H-2), 7.12 (d, 1H, J=8.3 Hz, H-1)

Example 12

3,16α-Dihydroxy-17-(1',2'-ethylene)-estra-1,3,5(10)-triene

Prepared from 3,16α-dihydroxy-17-(1',2'-ethylene)-estra-1,3,5(10)-triene, 3-O-dimethyl--thexylsilyl ether according to procedure B.

Yield: 50 mg (74 %)

R_f (5:1)=0.10

mp 227-32°C

MS-FAB: m/z = 298 (M^+)

^{1}H NMR ($(CD_3)_2$ SO) δ 0.24-0.40, 0.65 (2m, 4H, 17-ethylene), 0.76 (s, 3H, H-18), 4.08 (m, 1H, H-16), 4.35 (d, 1H, J=7.1 Hz, 16-OH), 6.44 (s, 1H, H-4), 6.50 (d, 1H, J=8.6 Hz, H-2), 7.02 (d, 1H, J=8.6 Hz, H-1), 9.00 (broad s, 1H, 3-OH)

Example 13

3-Hydroxy-17-keto-16α-methyl-estra-1,3,5(10)-triene, 3-O-dimethylthexylsilyl ether

Lithium diisopropylamide (2.8 ml, 4.2 mmol, 1.5 M THF-complex in c-hexane) was added to a solution of 3-Hydroxy-17-keto-estra-1,3,5(10)-triene, 3-O-dimethylthexylsilyl ether (1.50 g, 3.63 mmol) in dry THF (6 ml) under N_2 at 0°C. After stirring for 1 h the temperature was lowered to -78°C and MeI (270 µl, 4.3 mmol) was added. The reaction mixture was stirred at -78°C for 5 h, then at ambient temperature over night and was then partitioned in EtOAc/H_2O. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated at reduced pressure. The residue was purified by column chromatography (heptane-EtOAc, 20:1) to give the titel compound (800 mg, 52 %).

R_f (20:1)=0.23

^{1}H NMR ($CDCl_3$) δ 0.22 (s, 6H, -$Si(CH_3)_2$-), 0.94 (s, 3H, H-18), 0.94 (s, 6H, thexyl), 0.94 (d, 6H, J=6.8 Hz, thexyl), 1.14 (d, 1H, J=7.8 Hz, 16-Me), 6.58 (d, 1H, J=2.4 Hz, H-4), 6.62 (dd, 1H, J=2.4 Hz, 8.3 Hz, H-2), 7.13 (d, 1H, J=8.3 Hz, H-1)

Example 14

3-Hydroxy-16α/β-methyl-17-methylene-estra-1,3,5(10)-triene, 3-O-dimethylthexylsilyl ether

Potassium tert-butoxide (73 mg, 0.65 mmol) was added to a solution of methyltriphenyl-phosphonium bromide (300 mg, 0.84 mmol) in dry DMSO (1.8 ml) under N_2. After stirring for 20 min the temperature was raised to 75°C and a solution of 3-hydroxy-17-keto-16α-methyl-estra-1,3,5(10)-triene, 3-O-dimethylthexylsilyl ether (298 mg, 70 mmol) in dry THF (1.5 ml) was added. The reaction mixture was stirred at 75°C for 1.5 h and was then partitioned in Et_2O/H_2O. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. The residue was purified by column chromatography (heptane) to give the titel compound as a ca 1:1 epimeric mixture (85 mg, 28 %).

R_f (heptane)=0.24

^{1}H NMR ($CDCl_3$) δ 0.22 (s, 6H, $-Si(CH_3)_2-$), 0.84, 0.94 (2s, 3H, H-18), 0.94 (s, 6H, thexyl), 0.94 (d, 6H, J=6.8 Hz, thexyl), 1.10, 1.19 (2d, 3H, J=7.1 Hz, 16-Me), 4.68, 4.73 (2m, 2H, Hz, $=CH_2$), 6.56 (d, 1H, J=2.2 Hz, H-4), 6.62 (dd, 1H, J=2.2 Hz, 8.3 Hz, H-2), 7.13 (d, 1H, J=8.3 Hz, H-1)

Example 15

3,16α-Dihydroxy-16α,β-methyl-17-methylene-estra-1,3,5(10)-triene, 3-O-dimethyl--thexylsilyl ether

Prepared from 3-hydroxy-16α,β-methyl-17-methylene-estra-1,3,5(10)-triene, 3-O-dimethyl-thexylsilyl ether according to procedure A.

Yield: 35 mg (40 %)

R_f(10:1)=0.10

^1H NMR ($CDCl_3$) δ 0.22 (s, 6H, -$Si(CH_3)_2$ -), 0.87 (s, 3H, H-18), 0.94 (s, 6H, thexyl), 0.94 (d, 6H, J=6.8 Hz, thexyl), 1.48 (s, 3H, 16-Me), 4.85, 5.09 (2s, 2H, =CH_2), 6.55 (d, 1H, J=2.4 Hz, H-4), 6.61 (dd, 1H, J=2.4 Hz, 8.3 Hz, H-2), 7.13 (d, 1H, J=8.3 Hz, H-1)

Example 16

3,16α-Dihydroxy-16β-methyl-17-methylene-estra-1,3,5(10)-triene

Prepared from 3,16α-dihydroxy-16β-methyl-17-methylene-estra-1,3,5(10)-triene, 3-O-dimethyl-thexylsilyl ether according to procedure B.

Yield: 56 mg (78 %)

R_f (1:1)=0.47

mp 238-243°C

MS(FAB): m/z =298 (M^+)

^1H NMR ($CDCl_3$) δ ^1H NMR ($CDCl_3$) δ 0.87 (s, 3H, H-18), 1.49 (s, 3H, 16-Me), 4.53 (s, 1H, phenol), 4.86 (s, 1H, =CH_2), 5.10 (s, 1H, =CH_2), 6.57 (d, 1H, J=2.4 Hz, H-4), 6.64 (dd, 1H, J=2.4 Hz, 8.3 Hz, H-2), 7.18 (d, 1H, J=8.3 Hz, H-1)

Example 17

(17Z)-3-Hydroxy-19-norpregna-1,3,5(10),17(20)-tetraene, 3-O-dimethylthexylsilyl ether

Potassium tert-butoxide (325 mg, 2.90 mmol) was added to a solution of ethyltriphenyl-phosphonium bromide (1.08 g, 2.90 mmol) in dry DMSO (6.0 ml) under N_2. After stirring for 20 min the temperature was raised to 75°C and a solution of 3-hydroxy-17-keto-estra-1,3,5(10)-triene, 3-O-dimethylthexylsilyl ether (1.00g, 2.42 mmol) in dry THF (4.0 ml) was added. The reaction mixture was stirred at 75°C for 2.5 h. After cooling the reaction mixture was partitioned in Et_2O/H_2O and the organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. The residue was purified by column chromatography (heptane) to give the titel compound as a ca 1:1 epimeric mixture (85 mg, 28 %).

R_f (heptane)=0.2

^{1}H NMR ($CDCl_3$) δ 0.22 (s, 6H, -$Si(CH_3)_2$ -), 0.91 (s, 3H, H-18), 0.94 (s, 6H, thexyl), 0.94 (d, 6H, J=6.8 Hz, thexyl), 1.7 (m, 3H, H-21), 6.54 (d, 1H, J=2.6 Hz, H-4), 6.61 (dd, 1H, J=2.6 Hz, 8.7 Hz, H-2), 7.13 (d, 1H, J=8.7 Hz, H-1)

Example 18

(17E)-3,16α-Dihydroxy-19-norpregna-1,3,5(10),17(20)-tetraene, 3-O-dimethyl-thexylsilyl ether

Prepared from (17Z)-3-hydroxy-19-norpregna-1,3,5(10),17(20)-tetraene, 3-O-dimethyl--thexylsilyl ether according to procedure A.

Yield: 140 mg (51 %)

R_f (10:1)=0.07

^{1}H NMR ($CDCl_3$) δ 0.22 (s, 6H, -$Si(CH_3)_2$ -), 0.92 (s, 3H, H-18), 0.94 (s, 6H, thexyl), 0.94 (d, 6H, J=6.8 Hz, thexyl), 1.78 (d, 3H, J=7 Hz, H-21), 4.48 (s, 1H, H-16), 6.56 (d, 1H, J=2.2 Hz, H-4), 6.62 (dd, 1H, J=2.2 Hz, 8.6 Hz, H-2), 7.12 (d, 1H, J=8.6 Hz, H-1)

Example 19

(17E)-3,16α-Dihydroxy-19-norpregna-1,3,5(10),17(20)-tetraene

Prepared from (17E)-3,16α-dihydroxy-19-norpregna-1,3,5(10),17(20)-tetraene, 3-O-dimethyl-thexylsilyl ether according to procedure B.

Yield: 30 mg (84 %)

R_f (1:1)=0.39

mp 225-31°C

MS(FAB): *m/z* =298

^{1}H NMR ($CDCl_3$) δ 0.92 (s, 3H, H-18), 1.78 (d, 3H, J=7 Hz, H-21), 4.48 (s, 1H, H-16), 6.57 (d, 1H, J=2.6 Hz, H-4), 6.63 (dd, 1H, J=2.6 Hz, 8.5 Hz, H-2), 7.16 (d, 1H, J=8.5 Hz, H-1)

Example 20

Etyl (17E)-3-hydroxy-19-norpregna-1,3,5(10),17(20)-tetraene-21-oate, 3-O-dimethyl--thexylsilyl ether

Triethyl phosphonoacetate (ↄ.00 mL, 15.0 mmol) was added dropwise to a slurry of NaH (480 mg, ca 60 % in oil, 12 mmol) in dry dimethoxyethane (DME, 30 ml) under N_2. After 10 min stirring, a solution of 3-hydroxy-17-keto-estra-1,3,5(10)-triene, 3-dimethyl-thexylsilyl ether (2.064 g, 5.00 mmol) in dry DME (15 ml) was added. The temperature was raised to 90°C and the reaction mixture was then stirred over night. After cooling heptane (20 ml) was added and most of the DME was removed by evaporation at reduced pressure. The residue was partitioned in Et_2O/H_2O and the organic phase was then washed with brine, dried over Na_2SO_4, and concentrated at reduced pressure. The residue was purified by column chromatography (heptane-EtOAc, 50:1, 20:1) to give the titel compound as a white solid (1.494 mg, 62 %).

R_f (20:1)=0.30;

^{1}H NMR ($CDCl_3$) δ 0.22 (s, 6H, -$Si(CH_3)_2$ -), 0.86 (s, 3H, H-18), 0.94 (s, 6H, thexyl), 0.94 (d, 6H, J=6.8 Hz, thexyl), 1.29 (t, 3H, J=7.1 Hz, Et), 4.16 (q, 2H, J=7.1 Hz, Et), 5.59 (dd, 1H, J=2.4 Hz, 2.4 Hz, H-20), 6.55 (d, 1H, J=2.7 Hz, H-4), 6.61 (dd, 1H, J=2.7 Hz, 8.5 Hz, H-2), 7.12 (d, 1H, J=8.5 Hz, H-1)

Exampl 21

(17E)-3,21-Dihydroxy-19-norpregna-1,3,5(10),17(20)-tetraene, 3-O-dimethyl-thexylsilyl ether

Lithium triethylborohydride (6.0 mL, 1 M in THF, 6.0 mmol) was added to a solution of etyl (17E)-3-hydroxy-19-norpregna-1,3,5(10),17(20)-tetraene-21-oate, 3-O-dimethyl-

thexylsilyl ether (1.320 g, 2.73 mmol) in dry THF (6.0 mL) at 0°C under N_2. The reaction mixture was stirred for another 10 min and was then partitioned in Et_2O/ brine and acidified with 1 M HCl (ca 10mL). The organic phase was washed with brine, dried over Na_2SO_4, and concentrated at reduced pressure. The residue was purified by column chromatography (heptane-EtOAc, 5:1, 3:1) to give the titel compound as a white solid (1.048 mg, 87 %).

R_f (3:1)=0.27

^{1}H NMR ($CDCl_3$) δ 0.22 (s, 6H, -Si(CH_3)$_2$ -), 0.81 (s, 3H, H-18), 0.94 (s, 6H, thexyl), 0.94 (d, 6H, J=6.8 Hz, thexyl), 4.14(m, 2H, H-21), 5.29 (m, 1H, H-20), 6.54 (d, 1H, J=2.4 Hz, H-4), 6.61 (dd, 1H, J=2.4 Hz, 8.1 Hz, H-2), 7.13 (d, 1H, J=8.1 Hz, H-1)

Example 22

(17E)-3-Hydroxy-19-norpregna-1,3,5(10),17(20)-tetraene, 3-O-dimethylthexylsilyl ether

Methanesulfonic anhydride (52 mg, 0.3 mmol) was added to a solution of (17E)-3,21-dihydroxy-19-norpregna-1,3,5(10),17(20)-tetraene, 3-O-dimethylthexylsilyl ether (74 mg, 0.17 mmol) and 2,6-lutidine (46 µL, 0.4 mmol) in dry THF (0.5 mL) under N_2. After 5 min stirring, lithium triethylborohydride (500 µL, 1 M in THF, 0.50 mmol) was added. The reaction mixture was stirred for another 10 min and was then partitioned in Et_2O/ brine and acidified with 1 M HCl (ca 5 mL). The organic phase was washed with brine, $NaHCO_3$ (sat.) and brine again, dried over Na_2SO_4, and concentrated at reduced pressure. The residue was purified by column chromatography (heptane-EtOAc, 50:1) to give the titel compound as an oil (40 mg, 56 %).

R_f (50:1)=0.30

^{1}H NMR ($CDCl_3$) δ 0.21 (s, 6H, -Si(CH_3)$_2$ -), 0.77 (s, 3H, H-18), 0.94 (s, 6H, thexyl), 0.94 (d, 6H, J=7.1 Hz, thexyl), 1.56 (ddd, 3H, J=6.6 Hz, 1.5 Hz, 1.5 Hz, H-21), 5.08 (m, 1H, H-

20), 6.54 (d, 1H, J=2.7 Hz, H-4), 6.60 (dd, 1H, J=2.7 Hz, 8.3 Hz, H-2), 7.14 (d, 1H, J=8.3 Hz, H-1)

Example 23

(17Z)-3,16α-Dihydroxy-19-norpregna-1,3,5(10),17(20)-tetraene, 3-O-dimethyl-thexylsilyl ether

Prepared from (17E)-3-hydroxy-19-norpregna-1,3,5(10),17(20)-tetraene, 3-O-dimethyl--thexylsilyl ether according to procedure A.

Yield: 25mg (45 %)

R_f (5:1)=0.29

^{1}H NMR ($CDCl_3$) δ 0.21 (s, 6H, $-Si(CH_3)_2-$), 0.77 (s, 3H, H-18), 0.94 (s, 6H, thexyl), 0.94 (d, 6H, J=7 Hz, thexyl), 1.81 (d, 3H, J=7 Hz, H-21), 4.85 (m, 1H, H-16), 5.37 (dq, 1H, J=2 Hz, 7 Hz, H-20), 6.55 (d, 1H, J=2.7 Hz, H-4), 6.61 (dd, 1H, J=2.7 Hz, 8.2 Hz, H-2), 7.12 (d, 1H, J=8.2 Hz, H-1)

Example 24

(17Z)-3-Hydroxy-16-keto-19-norpregna-1,3,5(10),17(20)-tetraene, 3-O-dimethyl-thexylsilyl ether

The reaction according to Example 23 also provided the compound of this Example.

Yield: 20mg (36 %)

R_f (10:1)=0.19

^{1}H NMR ($CDCl_3$) δ 0.22 (s, 6H, $-Si(CH_3)_2-$), 0.94 (s, 6H, thexyl), 0.94 (d, 6H, J=6.8 Hz, thexyl), 1.06 (s, 3H, H-18), 1.89 (d, 3H, J=7.6 Hz, H-21), 6.54 (q, 1H, J=7.6 Hz, H-20), 6.56 (d, 1H, J=2.7 Hz, H-4), 6.63 (dd, 1H, J=2.7 Hz, 8.5 Hz, H-2), 7.12 (d, 1H, J=8.5 Hz, H-1)

Example 25

(17Z)-3,16α-Dihydroxy-19-norpregna-1,3,5(10),17(20)-tetraene

Prepared from (17Z)-3,16α-dihydroxy-19-norpregna-1,3,5(10),17(20)-tetraene, 3-O-dimethyl-thexylsilyl ether according to procedure B.

Yield: 11mg (82 %)

R_f (2:1)=0.26

mp 228-32°C

MS-FAB: m/z = 298 (M^+)

^{1}H NMR ($CDCl_3$) δ 0.77 (s, 3H, H-18), 1.81 (d, 3H, J=6.8 Hz, H-21), 4.57 (s, 1H, 3-OH), 4.85 (m, 1H, H-16), 5.38 (dq, 1H, J=1.7 Hz, 6.8 Hz, H-20), 6.57 (d, 1H, J=2.7 Hz, H-4), 6.63 (dd, 1H, J=2.7 Hz, 8.5 Hz, H-2), 7.16 (d, 1H, J=8.5 Hz, H-1)

Example 26

3,16α,17β-Trihydroxy-estra-1,3,5(10)-triene, 3,16α-bis(dimethylthexylsilyl ether)

Dimethylthexylchlorosilane (1.47 ml, 7.49 mmol) was added to a solution of 3,16α,17β-trihydroxy-estra-1,3,5(10)-triene (estriol, 1.00 g, 3.47 mmol) and imidazole (1.02 g, 15.0 mmol) in dry DMF (2.0 ml). The reaction mixture was stirred for 30 min and the raw product was then purified directly by column chromatography (heptane-EtOAc, 10:1) to give the title compound as an oil which crystallized on standing (1.95 g, 98 %).

R_f (10:1)=0.22

^{1}H NMR ($CDCl_3$) δ 0.11 (s, 3H, $-SiMe_2-$), 0.13 (s, 3H, $-SiMe_2-$), 0.21 (s, 6H, $-SiMe_2-$), 0.78 (s, 3H, H-18), 0.86 (s, 6H, thexyl), 0.90 (d, 6H, J=6.8 Hz, thexyl), 0.94 (s, 6H, thexyl), 0.94 (d, 6H, J=6.8 Hz, thexyl), 3.56 (t, 1H, J=5.4 Hz, H-17), 4.07 (m, 1H, H-16), 6.54 (d, 1H, J= 2.7 Hz, H-4), 6.60 (dd, 1H, J=2.7 Hz, 8.3 Hz, H-2), 7.11 (d, 1H, J=8.3 Hz, H-1)

Example 27

3,16α-Dihydroxy-17-keto-estra-1,3,5(10)-triene, 3,16α-bis(dimethyl-thexylsilyl ether)

N-methylmorfolin-N-oxide (300 mg, 2.22 mmol) and tetrapropylammonium perruthenate (TPAP, 40 mg, 0.11 mmol) were added to a solution of 3,16α,17β-trihydroxy-estra-1,3,5(10)-triene, 3,16α-bis(dimethyl-thexylsilyl ether) (790 mg, 1.38 mmol) in CH_2Cl_2 (3.0 ml). The solution was stirred for 6 h at room temperature and was then concentrated at reduced pressure. The residue was purified by column chromatography (heptane-EtOAc, 50:1, 20:1) to give the title compound as an oil (600 mg, 76 %).

R_f (20:1)=0.33

^{1}H NMR ($CDCl_3$) δ 0.15 (s, 3H, $-SiMe_2-$), 0.18 (s, 3H, $-SiMe_2-$), 0.22 (s, 6H, $-SiMe_2-$), 0.86 (s, 6H, thexyl), 0.88 (d, 3H, J=6.8 Hz, thexyl), 0.89 (d, 3H, J=6.8 Hz, thexyl), 0.93 (s, 3H, H-18), 0.94 (s, 6H, thexyl), 0.94 (d, 6H, J=6.8 Hz, thexyl), 4.36 (d, 1H, J=7.5 Hz, H-16), 6.55 (d, 1H, J= 2.7 Hz, H-4), 6.61 (dd, 1H, J=2.7 Hz, 8.3 Hz, H-2), 7.11 (d, 1H, J=8.3 Hz, H-1)

Example 28

17-Difluoromethylene-3,16α-dihydroxy-estra-1,3,5(10)-triene, 3,16α-bis(dimethyl--thexylsilyl ether)

Litium diisopropylamide (750 μl, 1.5 M THF-complex in hexane, 1.12 mmol) was added to a solution of $F_2CHPO(OEt)_2$ (215 mg, 1.14 mmol) in dry THF (1.0 ml) under N_2 at -78°C. After 5 min stirring, a solution of 3,16α-dihydroxy-17-keto-estra-1,3,5(10)-triene, 3,16α-bis(dimethyl-thexylsilyl ether) (173 mg, 0.30 mmol) in dry THF was added and the reaction mixture was stirred at -78°C for 1 h, then at 60°C over night. After cooling, the reaction mixture was diluted with Et_2O (100 ml) and acidified with 1M HCl. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated at reduced pressure. The residue (268 mg of a brown oil) was purified by column chromatography (heptane, then heptane-EtOAc, 50:1, then 20:1) to give the titel compound as an oil (102 mg, 56 %).

R_f (50:1)=0.33

^{1}H-NMR ($CDCl_3$) δ 0.11 (s, 6H, -$SiMe_2$-), 0.21 (s, 6H, -$SiMe_2$-), 0.82 (s, 6H, thexyl), 0.87 (2d, 6H, J=6 Hz, thexyl), 0.88 (s, 3H, H-18), 0.94 (s, 6H, thexyl), 0.94 (d, 6H, J=6.9 Hz, thexyl), 4.77 (dd, 1H, J=1.6 Hz, 5.2 Hz, H-16), 6.54 (d, 1H, J= 2.7 Hz, H-4), 6.61 (dd, 1H, J=2.7 Hz, 8.4 Hz, H-2), 7.11 (d, 1H, J=8.4 Hz, H-1)

Example 29

17-Difluoromethylene-3,16α-dihydroxy-estra-1,3,5(10)-triene

$NBu_4F{\cdot}(H_2O)_3$ (200 mg, 0.63 mmol) was added to a solution of 17-difluoromethylene-3,16α-dihydroxy-estra-1,3,5(10)-triene, 3,16α-bis(dimethyl-thexylsilyl ether) (100 mg, 0.165 mmol) in dry THF (1.0 ml). The reaction mixture was stirred for 2 h at 50°C and was then quenched by adding AcOH (100 μl). Concentration at reduced pressure was followed by purification by column chromatography (heptane-EtOAc, 3:1, 2:1) to give the title compound as a white solid (19 mg, 36 %):

R_f (2:1)=0.28;
mp 225-27°C;
MS-FAB: m/z = 320 (M^+);

^{1}H NMR ($CDCl_3$) δ 0.91 (s, 3H, H-18), 4.52 (s, 1H, 3-OH), 4.89 (m, 1H, H-16), 6.57 (d, 1H, J=2.7 Hz, H-4), 6.63 (dd, 1H, J=2.7 Hz, 8.5 Hz, H-2), 7.15 (d, 1H, J=8.5 Hz, H-1)

3-O-Alkylether derivatives

General procedure for 3-O-alkylation of 3,16α-dihydroxy-17-methylene-estra-1,3,5(10)-triene

3,16a-Dihydroxy-17-methylene-estra-1,3,5(10)-triene (0.32 mmol), alkyl iodide (0.42 mmol), Cs_2CO_3 (0.70 mmol) and dry DMF (0.5-1.0 mL) under dry nitrogen were stirred over night at 40-80°C. The volatiles were evaporated at reduced pressure and the residue

was partitioned between saturated NH_4Cl and EtOAc (2x10 mL). The organic phases were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated at reduced pressure. The residue was purified by column chromatography on silica (heptane-EtOAc, 5:1) to give the 3-O-alkylether.

The following 3-O-alkyl ethers were prepared:

Example 30

3,16α-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3-O-cyclopentyl ether

Yield: 59%; colourless crystalline solid

R_f (3:1)=0.25

MS(EI) *m/z* 352 (M^+)

^{1}H NMR ($CDCl_3$) δ 0.82 (s, 3H, H-18), 4.67-4.75 (m, 2H), 4.92 (d, 1H, J= 1.8 Hz, =CH_2), 5.08 (d, 1H, J=1.5 Hz, =CH_2), 6.60 (d, 1H, J= 2.6 Hz, H-4), 6.67 (dd, 1H, J= 8.4 Hz, J= 2.6 Hz, H-2), 7.18 (d, 1H, J= 8.4 Hz, H-1)

Example 31

3,16a-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3-O-methyl ether

Yield: 49%; colourless crystalline solid

R_f (2:1)=0.24

MS(EI) *m/z* 298 (M^+)

^{1}H NMR ($CDCl_3$) d 0.83 (s, 3H, H-18), 3.78 (s, 3H, -OCH_3), 4.69-4.75 (m, 1H, H-16), 4.93 (d, 1H, J= 2.4 Hz, =CH_2), 5.09 (d, 1H, J= 1.8 Hz, =CH_2), 6.64 (d, 1H, J= 2.7 Hz, H-4), 6.72 (dd, 1H, J= 8.4 Hz, J= 2.7 Hz, H-2), 7.22 (d, 1H, J= 8.7 Hz, H-1)

Ester and carbonic-acid ester derivatives

General procedure for 3-O-monoesterification of 3,16a-dihydroxy-17-methylene-*estra-1,3,5(10)-triene*:

An acid chloride or chloroformate ester (0.36 mmol) in dry dioxane (0.35 mL) was added during 15 minutes to a rapidly stirred mixture of 3,16a-dihydroxy-17-methylene-estra-1,3,5(10)-triene (0.090 g, 0.32 mmol), ground NaOH (0.035 g), tetrabutyıammonium hydrogen sulfate (2-4 mg) and dioxane (0.80 mL). After stirring at room temperature for 10-30 minutes saturated NH_4Cl (2 mL), water (0.5 mL) and EtOAc (10 mL) were added. The organic phase was separated, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated at reduced pressure. The residue was purified by column chromatography on silica (with the eluent indicated below) to give the title compound. Yields: 40-60 %.

The following 3-O-monoesters were prepared:

Example 32

3, 16a-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3-acetate

R_f (1:1)=0.31

^{1}H NMR ($CDCl_3$) d 0.83 (s, 3H, H-18), 2.28 (s, 3H, Ac), 4.72 (m, 1H, H-16), 4.93 (d, 1H, J=2.2 Hz, =CH_2), 5.09 (d, 1H, J=1.7 Hz, =CH_2), 6.80 (d, 1H, J=2.4 Hz, H-4), 6.85 (dd, 1H, J=2.4 Hz, 8.6 Hz, H-2), 7.29 (d, 1H, J=8.6 Hz, H-1)

Example 33

3,16α-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3-benzoate

R_f (3:1)=0.20

^{1}H NMR ($CDCl_3$) δ 0.85 (s, 3H, H-18), 4.73 (m, 1H, H-16), 4.94 (d, 1H, J=2.0 Hz, =CH_2), 5.10 (d, 1H, J=1.7 Hz, =CH_2), 6.93 (d, 1H, J=2.4 Hz, H-4), 6.98 (dd, 1H, J=2.4 Hz, 8.3 Hz, H-2), 7.35 (d, 1H, J=8.3 Hz, H-1), 7.51 (m, 2H, Bz), 7.63 (m, 1H, Bz), 8.20 (m, 2H, Bz)

Example 34

3, 16a-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3-hexanoate

R_f (1:1)=0.37

^{1}H NMR ($CDCl_3$) d 0.84 (s, 3H, H-18), 0.90-0.98 (m, 3H), 2.54 (t, J= 7.5 Hz, 2H), 4.69-4.76 (m, 1H, H-16), 4.91 (d, 1H, J= 2.4 Hz, =CH_2), 5.10 (d, 1H, J= 1.8 Hz, =CH_2), 6.80 (d, 1H, J= 2.4 Hz, H-4), 6.85 (dd, 1H, J= 8.4 Hz, J= 2.4 Hz, H-2), 7.30 (d, 1H, J= 8.4 Hz, H-1)

Example 35

3, 16a-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3-octadecanoate

R_f (2:1)=0.29

^{1}H NMR ($CDCl_3$) d 0.83 (s, 3H, H-18), 0.85-0.92 (m, 3H), 2.53 (t, J= 7.5 Hz, 2H), 4.68-4.76 (m, 1H, H-16), 4.92-4.94 ("d", 1H, =CH_2), 5.07-5.11 ("d", 1H, =CH_2), 6.77-6.80 (m, 1H, H-4), 6.81-6.86 (m, 1H, H-2) and 7.28 (d, 1H, J= 9.0 Hz, H-1)

Example 36

3, 16α-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3-methylcarbonate

R_f (2:1)=0.19

^{1}H NMR ($CDCl_3$) d 0.83 (s, 3H, H-18), 3.89 (s, 3H, $-OCH_3$), 4.68-4.75 (m, 1H, H-16), 4.93 (d, 1H, J=2.1 Hz, $=CH_2$), 5.09 (d, 1H, J=1.8 Hz, $=CH_2$), 6.88 (d, 1H, J= 2.4 Hz, H-4), 6.93 (dd, 1H, J= 8.4 Hz, J= 2.4 Hz, H-2), 7.29 (d, 1H, J= 8.4 Hz, H-1)

Example 37

3, 16a-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3-butylcarbonate

R_f (1:1)=0.45

^{1}H NMR ($CDCl_3$) d 0.83 (s, 3H, H-18), 0.97 (t, J= 7.2 Hz, 3H), 4.24 (t, J= 6.6 Hz, 2H), 4.68-4.75 (m, 1H, H-16); 4.92 (d, 1H, J= 1.8 Hz, $=CH_2$), 5.08 (d, 1H, J= 1.2 Hz, $=CH_2$), 6.89 (d, 1H, J= 2.4 Hz, H-4), 6.94 (dd, 1H, J= 8.4 Hz, J= 2.4 Hz, H-2) and 7.29 (d, 1H, J= 8.1 Hz, H-1)

Example 38

3, 16a-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3-benzylcarbonate

R_f (2:1)=0.21

^{1}H NMR ($CDCl_3$) d 0.82 (s, 3H, H-18), 4.68-4.74 (m, 1H, H-16), 4.92 (d, 1H, J= 1.8 Hz, $=CH_2$), 5.08 (d, 1H, J= 1.5 Hz, $=CH_2$), 5.25 (s, 2H, OCH_2Ph), 6.88 (d, 1H, J= 2.4 Hz, H-4), 6.94 (dd, 1H, J= 8.7 Hz, J= 2.7 Hz, H-2), 7.29 (d, 1H, J= 8.4 Hz, H-1), 7.34-7.46 (m, 5H, C_6H_5-)

General procedure for 16α-O-monoesterification of 3,16α-dihydroxy-17-methylene-estra-1,3,5(10)-triene:

An ester anhydride or ester chloride (1.1 mmol) was added to a solution of 3,16α-dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3-O-dimethylthexylsilyl ether (1.0 mmol) and N,N-dimethylaminopyridine (1.5 mmol) in CH_2Cl_2 (1.5 mL). The reaction mixture was stirred for 1-4 h and was then concentrated at reduced pressure. The residue was filtered through a short silica gel column (heptane-EtOAc mixtures as eluents). The filtrate was concentrated at reduced pressure and the residue was treated according to Procedure B. Yields: 60-80 %.

The following 16α-O-monoester derivatives were prepared:

Example 39

3,16α-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 16α-acetate

R_f (5:1)=0.17

^{1}H NMR ($CDCl_3$) δ 0.85 (s, 3H, H-18), 2.11 (s, 3H, Ac), 4.64 (s, 1H, phenol), 4.94 (d, 1H, J=2.0 Hz, =CH_2), 4.97 (d, 1H, J=1.7 Hz, =CH_2), 5.72 (broad d, 1H, J=7.8 Hz, H-16), 6.57 (d, 1H, J=2.7 Hz, H-4), 6.63 (dd, 1H, J=2.7 Hz, 8.6 Hz, H-2), 7.16 (d, 1H, J=8.6 Hz, H-1)

Example 40

3,16α-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 16α-hexanoate

R_f (5:1)=0.22

^{1}H NMR ($CDCl_3$) δ 0.84 (s, 3H, H-18), 0.90 (t, 3H, J=7 Hz), 2.35 (t, 2H, J=7.5 Hz), 4.93 (d, 1H, J=2.1, Hz, =CH_2), 4.95 (d, 1H, J=1.8 Hz, =CH_2), 5.73 (d, 1H, J=6.9 Hz, H-16), 6.57 (d, 1H, J=2.7 Hz, H-4), 6.65 (dd, 1H, J=2.7 Hz, 8.4 Hz, H-2), 7.15 (d, 1H, J=8.4 Hz, H-1)

Example 41

3,16α-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 16α-octadecanoate

R_f (5:1)=0.23

^{1}H NMR ($CDCl_3$) δ 0.86 (s, 3H, H-18), 0.88 (t, 3H, J=7 Hz), 2.34 (t, 2H, J=7.5 Hz), 4.55 (s, 1H, phenol), 4.93 (d, 1H, J=2.3, Hz, =CH_2), 4.95 (d, 1H, J=1.7 Hz, =CH_2), 5.73 (broad d, 1H, J=6.3 Hz, H-16), 6.56 (d, 1H, J=2.9 Hz, H-4), 6.64 (dd, 1H, J=2.9 Hz, 8.2 Hz, H-2), 7.16 (d, 1H, J=8.2 Hz, H-1)

Example 42

3,16α-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 16α-benzoate

R_f (5:1)=0.12

^{1}H NMR ($CDCl_3$) δ 0.92 (s, 3H, H-18), 4.53 (s, 1H, phenol), 4.99 (d, 1H, J=2.1, Hz, =CH_2), 5.07 (d, 1H, J=1.8 Hz, =CH_2), 5.95 (broad d, 1H, J=6.6 Hz, H-16), 6.57 (d, 1H, J=2.7 Hz, H-4), 6.64 (dd, 1H, J=2.7 Hz, 8.7 Hz, H-2), 7.18 (d, 1H, J=8.7 Hz, H-1), 7.45 (t, 2H, J=7.4 Hz, Ph), 7.57 (m, 1H, Ph), 8.08 (d, 2H, J=7.4 Hz, Ph)

Example 43

3,16α-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 16α-methylcarbonate

R_f (3:1)=0.27

^{1}H NMR ($CDCl_3$) δ 0.85 (s, 3H, H-18), 3.81 (s, 3H, OMe), 4.76 (s, 1H, phenol), 5.00 (d, 1H, J=2.2 Hz, =CH_2), 5.05 (d, 1H, J=1.7 Hz, =CH_2), 5.59 (m, 1H, H-16), 6.57 (d, 1H, J=2.7 Hz, H-4), 6.63 (dd, 1H, J=2.7 Hz, 8.3 Hz, H-2), 7.16 (d, 1H, J=8.3 Hz, H-1)

Example 44

3,16α-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 16α-n-butylcarbonate

R_f (5:1)=0.16

^{1}H NMR ($CDCl_3$) δ 0.85 (s, 1H, H-18), 0.94 (t, J=7.5 Hz, 3H), 4.17 (t, 2H, J=6.6 Hz), 4.99 (s, 1H, =CH_2), 5.10 (s, 1H, =CH_2), 5.60 (m, 1H, H-16), 6.57 (d, 1H, J=2.7 Hz, H-4), 6.62 (dd, 1H, J=2.7 Hz, 8.5 Hz, H-2), 7.16 (d, 1H, J=8.5 Hz, H-1)

Example 45

3,16α-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 16α-benzylcarbonate

R_f(5:1)=0.14

^{1}H NMR ($CDCl_3$) δ 0.85 (s, 1H, H-18), 4.98 (d, 1H, J=1.8 Hz, =CH_2), 5.09 (d, 1H, J=1.5 Hz, =CH_2), 5.19 (s, 2H, benzyl), 5.62 (m, 1H, H-16), 6.56 (d, 1H, J=2.7 Hz, H-4), 6.63 (dd, 1H, J=2.7 Hz, 8.4 Hz, H-2), 7.15 (d, 1H, J=8.4 Hz, H-1), 7.33-7.42 (m, 5H, Ph)

General procedure for 3-O,16α-O-diesterification of 3,16α-dihydroxy-17-methylene-estra-1,3,5(10)-triene:

An ester anhydride or ester chloride (3.0 mmol) was added to a solution of 3,16α-dihydroxy-17-methylene-estra-1,3,5(10)-triene (1.0 mmol) and N,N-dimethyl-aminopyridine (4.0 mmol) in CH_2Cl_2 (1.5 mL). The reaction mixture was stirred for 1-3 h and was then concentrated at reduced pressure. The residue was purified by column chromatography (heptane-EtOAc) to give the 3,16α-diester derivatives. Yields ca 70-80 %.

The following 3-O,16α-O-diesters were prepared:

Example 46

3,16α-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3,16α-diacetate

R_f (10:1)=0.33

^{1}H NMR ($CDCl_3$) δ 0.85 (s, 3H, H-18), 2.10 (s, 3H, Ac), 2.28 (s, 3H, Ac), 4.95 (d, 1H, J=2.0 Hz, =CH_2), 4.98 (d, 1H, J=1.5 Hz, =CH_2), 5.73 (broad d, 1H, J=7.8 Hz, H-16), 6.80 (d, 1H, J=2.4 Hz, H-4), 6.85 (dd, 1H, J=2.4 Hz, 8.6 Hz, H-2), 7.29 (d, 1H, J=8.6 Hz, H-1)

Example 47

3,16α-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3,16α-dihexanoate

R_f (5:1)=0.61

^{1}H NMR ($CDCl_3$) δ 0.86 (s, 1H, H-18), 0.91 (m, 6H), 2.34 (t, 2H, J=7.5 Hz), 2.53 (t, 2H, J=7.5 Hz), 4.93 (d, 1H, J=2.2 Hz, =CH_2), 4.95 (d, 1H, J=1.7 Hz, =CH_2), 5.73 (broad d, 1H, J=6.9 Hz, H-16), 6.78 (d, 1H, J=2.5 Hz, H-4), 6.84 (dd, 1H, J=2.5 Hz, 8.4 Hz, H-2), 7.29 (d, 1H, J=8.4 Hz, H-1)

Example 48

3,16α-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3,16α-dihexadecanoate

R_f (20:1)=0.27

^{1}H NMR ($CDCl_3$) δ 0.84-0.92 (m, 9H), 2.34 (t, 2H, J=7.5 Hz), 2.53 (t, 2H, J=7.5 Hz), 4.93 (d, 1H, J=2.2 Hz, =CH_2), 4.95 (d, 1H, J=1.7 Hz, =CH_2), 5.73 (broad d, 1H, J=7.6 Hz, H-16), 6.78 (d, 1H, J=2.4 Hz, H-4), 6.84 (dd, 1H, J=2.4 Hz, 8.5 Hz, H-2), 7.29 (d, 1H, J=8.5 Hz, H-1)

Example 49

3,16α-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3,16α-dibenzoate

R_f (5:1)=0.34

^{1}H NMR ($CDCl_3$) δ 0.93 (s, 1H, H-18), 5.00 (d, 1H, J=2Hz, =CH_2), 5.08 (d, 1H, J=2 Hz, =CH_2), 5.96 (d, 1H, J=7.5 Hz, H-16), 6.94 (d, 1H, J=2.4 Hz, H-4), 6.99 (dd, 1H, J=2.4 Hz, 8.7 Hz, H-2), 7.46 (d, 1H, J=8.7 Hz, H-1), 7.30-7.70 (m, 4H), 8.07-8.22 (m, 6H)

Example 50

3,16α-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3,16α-di(metylcarbonate)

R_f (5:1)=0.24

^{1}H NMR ($CDCl_3$) δ 0.85 (s, 1H, H-18), 3.81 (s, 3H, -OCH_3), 3.89 (s, 3H, -OCH_3), 5.03 (d, 1H, J=2.2 Hz, =CH_2), 5.10 (d, 1H, J=1.7 Hz, =CH_2), 5.59 (m, 1H, H-16), 6.89 (d, 1H, J=2.4 Hz, H-4), 6.93 (dd, 1H, J=2.4 Hz, 8.4 Hz, H-2), 7.29 (d, 1H, J=8.4 Hz, H-1)

Example 51

3,16α-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3,16α-di(n-butylcarbonate)

R_f (5:1)=0.50

^{1}H NMR ($CDCl_3$) δ 0.85 (s, 1H, H-18), 0.96 (m, 6H), 4.17 (t, 2H, J=6.8 Hz), 4.24 (t, 2H, J=6.8 Hz), 4.99 (d, 1H, J=2.1 Hz, =CH_2), 5.11 (d, 1H, J=1.8 Hz, =CH_2), 5.60 (m, 1H, H-16), 6.89 (d, 1H, J=2.4 Hz, H-4), 6.93 (dd, 1H, J=2.4 Hz, 8.5 Hz, H-2), 7.28 (d, 1H, J=8.5 Hz, H-1)

Example 52

3,16α-Dihydroxy-17-methylene-estra-1,3,5(10)-triene, 3,16α-di(benzylcarbonate)

R_f (5:1)=0.23

^{1}H NMR ($CDCl_3$) δ 0.84 (s, 1H, H-18), 4.99 (d, 1H, J=2Hz, =CH_2), 5.10 (d, 1H, J=2 Hz, =CH_2), 5.19, 5.26 (2s, 4H, benzyl), 5.62 (m, 1H, H-16), 6.88 (d, 1H, J=2.4 Hz, H-4), 6.94 (dd, 1H, J=2.4 Hz, 8.4 Hz, H-2), 7.26-7.43 (m, 11H, H-1, Ph)

Example 53

17-(1',2'-Ethylene)-3-hydroxy-16-keto-estra-1,3,5(10)-trienene, 3-dimethyl-thexylsilyl ether

NaH (55-65 % in oil, 120 mg, 3.0 mmol) was washed under N_2 three times with dry n-hexane and dried at reduced pressure. Dry DMSO (3.0 mL) was then added followed by finely ground and vacuum-dried trimethylsulfoxonium iodide (662 mg, 3.0 mmol). The mixture was stirred under nitrogen until the hydrogen gas evolution ceased and the solution became clear (within 20 min), then transferred dropwise to a stirred solution of 3-hydroxy-16-keto-17-metylene-estra-1,3,5(10)-trienene, 3-dimethyl-thexylsilyl ether (1.27 g, 3.0 mmol) in dry DMSO (2.0 mL) and dry THF (2.0 mL. After stirring for 2 h at room temperature EtOAc (20 mL) was added and the solution was washed five times with 5% aqueous NaCl. Then the organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated at reduced pressure. The residual yellow oil was purified by column chromatography (toluene as eluent) to give the title compound (230 mg, 18 %) as a colourless oil, which solidified in the cool.

TLC: R_f(toluene)=0.21

MS(EI) m/z 438 (M^+)

^{1}H NMR ($CDCl_3$) δ 0.23 (s, 6H), 0.65-0.70 (m, 1H), 0.76-0.81 (m, 1H), 0.95 (s, 3H), 0.96 (s, 6H), 0.97 (d, 6H), 1.02-1.07 (m, 1H), 1.19-1.24 (m, 1H), 1.36-1.40 (m, 2H), 1.44-1.52

(m, 1H), 1.56-1.78 (m, 3H), 1.83-1.92 (m, 2H), 2.21 (app dd, 1H, J=14 Hz, J=17 Hz), 2.35-2.44 (m, 3H), 2.81-2.93 (m, 2H), 6.58 (d, 1H, J=2.4 Hz), 6.63 (dd, 1H, J=8.3 Hz, J=2.7 Hz), 7.13 (d, 1H, J=8.5 Hz).

Pharmaceutical preparations

The novel steroidal estrogens according to the invention may be administered by transdermal patches, orally or intranasally .

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level as the most appropriate for a particular patient.

The pharmaceutical preparation comprising a compound of the invention may be a patch, a tablet, a capsule or a nasal spray.

In a transdermal device the novel estrogen is dissolved in suitable solvents (e.g. ethanol, propylene glycol) comprising a thickener. The patch further comprises a current backing membrane and a silicone release liner. The device may also be constructed with a rate control membrane.

When administered orally the novel estrogens may be administered as a conventional tablet or gelatin capsule. The tablet may comprise usual tablet constituents, e.g. diluents (such as lactose), binders (such as polyvidone), lubricants (such as magnesium stearate) and disintegrants (such as microcrystalline cellulose). The estrogen substance may also be mixed with diluents and filled into gelatin capsules.

When administered intranasally by means of a nasal spray, the formulation is a suspension of the novel estrogens of the invention in water comprising a thickener, a surface active ingredient and a preservative.

Biological evaluation

The anti-inflammatory and immunosuppressive potencies were evaluated in animal models for autoimmune diseases.

For rheumatoid arthritis the type II collagen induced arthritis (CIA) model in mice was used (Jansson, L., Holmdahl, R., Clin. Exp. Immunol. (1992), 89, 446-451).

Mouse CIA model

In this model F1 generation (females) between B10Q and DBA/1 mice are used. The mice are ovariectomized two weeks before induction of arthritis.

Immunisation is performed using collagen type II (purified from rat chondrosarcoma) emulsified in Freunds complete adjuvant.

The treatment is performed by subcutaneous administration of estrogen analogues (0.1 ml) in Miglyol oil vehicle or solutol. The mice are treated on day 14, 17, 21, 24, 28, and 32 respectively, after immunisation. Day 36 is the end of the experiment, and the arthritis symptoms start approximately on day 14-20.

Evaluation of sex-related effects is performed by observing the stage of estrus by vaginal smears 17, 21, 24, 30, and 36 days after immunisation. At day 36 which is the end of the experiment, the weight of the uterus is recorded.

The evaluation of the arthritic effect is performed by observing the joints of the paws and legs for swelling and erythema every third day after immunisation.

The development of arthritis was evaluated continuously for each group as the incidence (%) of affected animals. The cumulative incidence (area under the curve, auc) was calculated in each group up to day 30. The anti-arthritic effect of estrogen treatment was expressed as the auc of treated animals relative the auc of the control group ($auc_{treated\ animals}/auc_{control}$, %), i.e. 100 % denotes no anti-arthritic effect and 0 % denotes total blockade of arthritic development. The antiarthritic effect is related in dose-response studies to the extent of uterine proliferation, and it is possible to estimate the difference in .mmunosuppressive/sex hormonal profiles.

The novel steroidal estrogens of the present invention, derivatives of 17-alkylidene-3,16-dihydroxy-estra-1,3,5(10)-trienes, show very low "sex hormonal" activity while retaining their anti-inflammatory and immunosuppressive effects.

The rat-CIA model

Still another animal model for the evaluation of the anti-inflammatory and immunosuppressive effects is the rat CIA model.

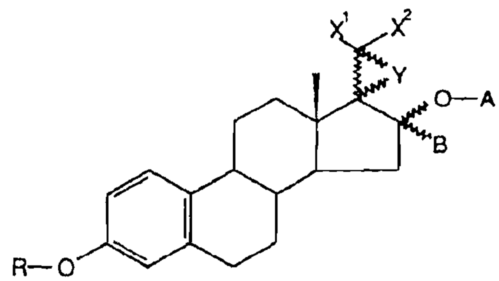
In this model female rats of the Dark Agouti strain are used. The rats are ovarieectomized two weeks before induction of arthritis.

Immunisation is performed using the same protocols as for CIA in mice, but with Freunds incomplete adjuvant.

Evaluation of the arthritic and sex-related effects are the same as in the mouse model. The length of the rat CIA-experiment is 21 days.

Claims

1. A compound according to the formula I



I

wherein

A is hydrogen, C_2-C_{18} alkanoyl, (C_6 aryl)carbonyl, C_2-C_{19} alkoxycarbonyl, or (C_6 aryloxy)carbonyl, or a protecting group;

B is hydrogen, methyl, or ethyl;

R is hydrogen, a straight, branched or cyclic C_1-C_6 alkyl, C_2-C_{18} alkanoyl, (C_6 aryl)carbonyl, C_2-C_{19} alkoxycarbonyl, (C_6 aryloxy)carbonyl, or a protecting group;

X^1 is hydrogen, methyl, ethyl or halogen;
X^2 is hydrogen, methyl, ethyl or halogen; and

Y is methylene or a single bond;

and pharmaceutically acceptable salts thereof;

the compounds

(17E)-16α-Acetoxy-3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraene;

(17E)-16α-Hydroxy-3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraene;

(17E)-16β-Hydroxy-3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraene;

being excluded.

2. A compound according to claim 1, wherein

A is hydrogen, or C_2-C_6 alkanoyl;
B is hydrogen, or methyl;
R is hydrogen, a straight, branched or cyclic C_1-C_6 alkyl, C_2-C_{18} alkanoyl, (C_6 aryl)carbonyl, C_2-C_{19} alkoxycarbonyl, (C_6 aryloxy)carbonyl, or a protecting group;

X^1 is hydrogen, methyl, or fluorine;
X^2 is hydrogen, methyl, or fluorine; and
Y is a methylene group or a single bond.

3. A compound according to claim 1, wherein

A is hydrogen or C_2-C_6 alkanoyl;
B is hydrogen;
R is hydrogen, a straight, branched or cyclic C_1-C_6 alkyl, C_2-C_{18} alkanoyl, (C_6 aryl)carbonyl, C_2-C_{19} alkoxycarbonyl, (C_6 aryloxy)carbonyl, or a protecting group;

X^1 is hydrogen, or fluorine;
X^2 is hydrogen, or fluorine; and
Y is a single bond or a methylene group

4. A compound according to claim 1, wherein

A is hydrogen;

B is hydrogen;

R is hydrogen or C_2-C_6 alkanoyl;

$\mathbf{X^1}$ is hydrogen;

$\mathbf{X^2}$ is hydrogen;

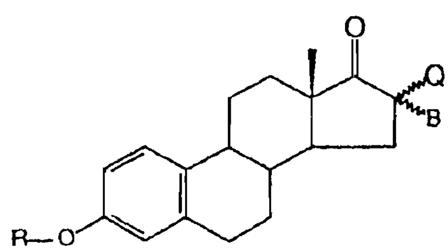
Y is a single bond; and

the 16-OH group is in the α-position.

5. A compound of the formula I according to claim 1, being 3,16α-dihydroxy-17-methylene-estra-1,3,5(10)triene.

6. A process for the preparation of a compound according to formula I of claim 1, whereby

(i) a compound of the formula II



II

wherein

A is hydrogen, C_2-C_{18} alkanoyl, (C_6 aryl)carbonyl, C_2-C_{19} alkoxycarbonyl, (C_6 aryloxy)carbonyl, or a protecting group;

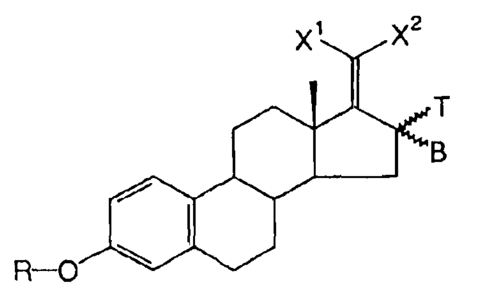
B is hydrogen, methyl, or ethyl;

R is hydrogen, a straight, branched or cyclic C_1-C_6 alkyl, C_2-C_{18} alkanoyl, (C_6 aryl)carbonyl, C_2-C_{19} alkoxycarbonyl, (C_6 aryloxy)carbonyl, or a protecting group; and

Q is (O-A) or hydrogen, wherein O is oxygen and A is as defined above;

wherein the 3-O-position being optionally protected,

is reacted with a phosphorous ylide or with the salt of a stabilized alkylphosphonate, optionally followed by the reduction of the adduct when a stabilized alkyl phosphonate is used, giving a compound of the formula III



III

wherein

A is hydrogen, C_2-C_{18} alkanoyl, C_6 aroyl, C_2-C_{19} alkoxycarbonyl, (C_6 aryloxy)carbonyl, or a protecting group;

B is hydrogen, methyl, or ethyl;

R is hydrogen, a straight, branched or cyclic C_1-C_6 alkyl, C_2-C_{18} alkanoyl, (C_6 aryl)carbonyl, C_2-C_{19} alkoxycarbonyl, (C_6 aryloxy)carbonyl, or a protecting group;

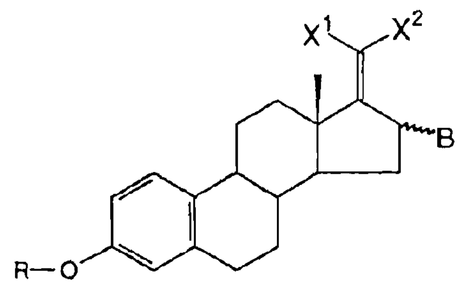
X^1 is hydrogen, methyl, ethyl or halogen; and

X^2 is hydrogen, methyl, ethyl or halogen;

T is (O-A) or hydrogen, wherein O is oxygen and A is as defined above;

or

(ii) a compound of the formula IV



IV

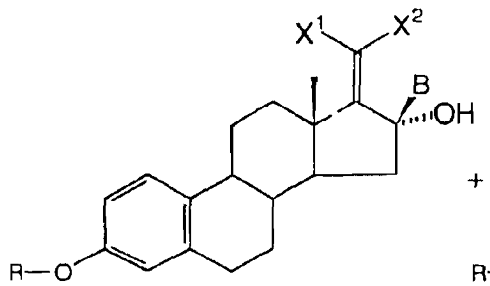
wherein

B is hydrogen, methyl, or ethyl;

R is hydrogen, a straight, branched or cyclic C_1-C_6 alkyl, C_2-C_{19} alkanoyl, (C_6 aryl)carbonyl, C_2-C_{19} alkoxycarbonyl, (C_6 aryloxy)carbonyl, or a protecting group; and

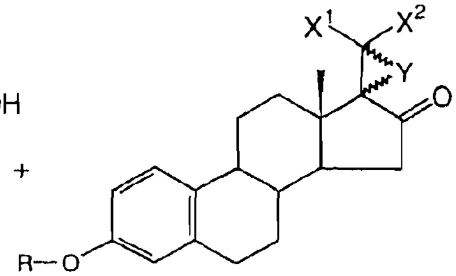
X^1 and X^2 is each and individually methyl, ethyl or hydrogen;

is subjected to a SeO_2-oxidation to achieve the 16-OA functionality, giving the 16α-OH compound of the formula V selectively together with the 16-keto compound of the formula VI



V

+



VI

wherein

B is hydrogen, methyl, or ethyl;

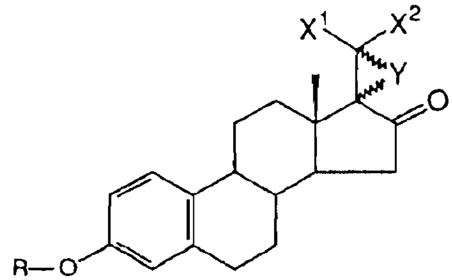
R is hydrogen, a straight, branched or cyclic C_1-C_6 alkyl, C_2-C_{18} alkanoyl, (C_6 aryl)carbonyl, C_2-C_{19} alkoxycarbonyl, (C_6 aryloxy)carbonyl, or a protecting group;

X^1 and X^2 is each and individually hydrogen, methyl or ethyl; and
Y is a single bond.

(iii) the 16-keto compound of the formula VI is subjected to a nucleophile in an inert solvent, or reduced, giving the 16β-hydroxy compound of the formula I wherein Y is a single bond.

7. A process according to claim 6, further c h a r a c t e r i z e d in that a cyclopropane moiety is introduced by reacting a compound of the formula I or VI wherein Y is a single bond, with a cyclopropanation reagent, optionally in the presence of a metal promotor, giving a compound of the formula I wherein Y is a methylene group or of the formula VI wherein Y is a methylene group.

8. A compound of the formula VI



VI

wherein

R is hydrogen, a straight, branched or cyclic C_1-C_6 alkyl, C_2-C_{18} alkanoyl, (C_6 aryl)carbonyl, C_2-C_{19} alkoxycarbonyl, (C_6 aryloxy)carbonyl, or a protecting group;
Y is a single bond or methylene; and
X^1 and X^2 is each and independently hydrogen, methyl, ethyl, or halogen,

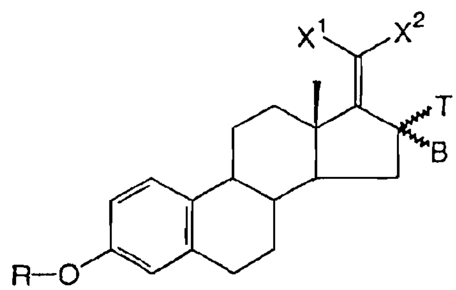
the compounds
16-keto-3-methoxy-17-methylene-estra-1,3,5(10)-triene; and
(17E)-16-keto-3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraene;

being excluded.

9. A compound of the formula VI according to claim 8, being

3-Hydroxy-16-keto-17-methylene -estra-1,3,5(10)-triene, 3-O-dimethyl-thexylsilyl ether; or (17Z)-3-Hydroxy-16-keto-19-norpregna-1,3,5(10),17(20)-tetraene, 3-O-dimethylthexylsilyl ether.

10. A compound of the formula III



III

wherein

A is hydrogen, C_2-C_{18} alkanoyl, (C_6 aryl)carbonyl, C_2-C_{19} alkoxycarbonyl, (C_6 aryloxy)carbonyl, or a protecting group;

B is hydrogen, methyl, or ethyl;

R is hydrogen, a straight, branched or cyclic C_1-C_6 alkyl, C_2-C_{19} alkanoyl, (C_6 aryl)carbonyl, C_2-C_{19} alkoxycarbonyl, (C_6 aryloxy)carbonyl, or a protecting group;

X^1 is hydrogen, methyl, ethyl or halogen;
X^2 is hydrogen, methyl, ethyl or halogen; and
T is hydrogen.

11. A compound of the formula III according to claim 10, being

3-Hydroxy-17-methylene-estra-1,3,5(10)-triene, 3-O-dimethylthexylsilyl ether;
3-Hydroxy-16α/β-methyl-17-methylene-estra-1,3,5(10)-triene, 3-O-dimethylthexylsilyl ether;
(17Z)-3-Hydroxy-19-norpregna-1,3,5(10),17(20)-tetraene, 3-O-dimethylthexylsilyl ether; or
(17E)-3-Hydroxy-19-norpregna-1,3,5(10),17(20)-tetraene, 3-O-dimethylthexylsilyl ether.

12. A compound according to claim 1, for use in therapy.

13. A compound according to claim 1, for use in the treatment of autoimmune disorders.

14. A compound according to claim 13, wherein the autoimmune disorder is rheumatoid arthritis or multiple sclerosis.

15. Use of a compound of the formula I according to claim 1, for the manufacture of a medicament for use in the treatment of autoimmune disorders such as rheumatoid arthritis and multiple sclersosis.

16. A pharmaceutical composition comprising a compound of the formula I according to claim 1 as active ingredient, together with a pharmaceutically acceptable carrier.

17. A method for the treatment of autoimmune disorders, whereby an effective amount of a compound of the formula I according to claim 1 is administered to a subject suffering from said autoimmune disorder.

18. A method according to claim 17, wherein the autoimmune disorder is rheumatoid arthritis or multiple sclerosis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/01028

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07J 53/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Lancet, Mars 1978, Sally J. Wingrave, "Reduction in incidence of rheumatoid arthritis associated with oral contraceptives", page 569 - page 571 --	1-7,12-16
A	Lancet, October 1982, J.P. Vandenbroucke, "Oral contraceptives and rheumatoid arthritis: further evidence for a preventive effect", page 839 - page 842 --	1-7,12-16

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 November 1996	04 -12- 1996
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/01028

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	American neurological association. Transactions, Volume 94, 1969, Barry G. Arnason et al, "Effects of Estrogen, Progestin and Combined Estrogen-Progestin Oral Contraceptive Preparations on Experimental Allergie Encephalomyelitis" page 54 - page 58 --	1-7,12-16
A	Arthritis and Rheumatism, Volume 16, No 2, 1973, Sara Ellen Walker et al, "Influence of Natural and Synthetic Estrogens on the Course of Autoimmune Disease in the NZB/NZW Mouse" page 231 - page 239 --	1-7,12-16
X	US 4977147 A (PETER JUNGBLUT ET AL), 11 December 1990 (11.12.90) --	10
X	US 5124321 A (PETER JUNGBLUT ET AL), 23 June 1992 (23.06.92) --	10
X	Journal of the American Chemical Society, Volume 98, No 2, January 1976, Dennis L. Lichtenberger et al, "New Synthetic Reactions. Catalytic vs. Stoichiometric Allylic Alkylation. Stereocontrolled Approach to Steroid Side Chain" page 630 - page 632 -- --------	10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/01028

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 17-18
because they relate to subject matter not required to be searched by this Authority, namely:
A method for treatment of the human or animal body by therapy, see rule 39.1.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
[ ] The additional search fees were accompanied by the applicant's protest.
[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/10/96

International application No.
PCT/SE 96/01028

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A- 4977147	11/12/90	AU-A-	2665388	08/06/89
		CA-A-	1329770	24/05/94
		DE-A-	3741801	15/06/89
		EP-A-	0320437	14/06/89
		JP-A-	1197438	09/08/89
US-A- 5124321	23/06/92	AU-A-	2665288	08/06/89
		CA-A-	1324374	16/11/93
		DE-A-	3741800	15/06/89
		DE-A-	3874865	29/10/92
		EP-A,B-	0320438	14/06/89
		SE-T3-	0320438	
		ES-T-	2045176	16/01/94
		JP-A-	1193295	03/08/89

Form PCT/ISA/210 (patent family annex) (July 1992)